

REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and these remarks.

I. Status of the Claims

Withdrawn claims 30-36 have been canceled. No other amendments and no new matter has been added. Upon entry of the foregoing amendment, claims 1-14, 20-27 and 29 will be pending.

II. Interview Summary

Applicants thank Examiner Cook for her very helpful discussion with Applicants' representative, Victoria Rutherford (Reg. No. 52,253), on December 5, 2008. Clarification was provided regarding the rejections such that these issues can be more fully addressed herein, as noted in the remarks below. Examiner Cook also kindly agreed to provide timely feedback after her consideration of this Reply, in order that Applicants may take necessary steps to keep this application pending before the statutory deadline, if needed. Applicants appreciate the Examiner's helpfulness and provide the following remarks in view of the outstanding Office Action and subsequent Interview.

III. Claim Rejections

A. *Previously overcome rejections*

Applicants thank the Examiner for withdrawing the previous rejections based on Houk, *Analytical Chem.* (1980) 52: 2283-89.

Applicants further note that all of the presently cited references were invoked in the Office Action of June 5, 2007, and overcome with the Reply filed October 31, 2007, as noted in the subsequent action of January 11, 2008. Anbar was first cited in the Office Action dated October 20, 2006, as part of an obviousness rejection in combination with Cais, which was withdrawn in the subsequent Office Action.

Although the Examiner asserts that Applicants' amendments necessitated these rejections, she does not explain how the minor revisions in question, put forward after the

presently cited art was overcome, somehow have returned these references to pertinence, making them re-applicable. The present claims differ from those deemed free of this same cited art only in that the tag further comprises a linker moiety and that recited kit contains instructions and packaging means. Certainly, the linker moiety does not alter the fact that the tag comprises at least one isotope of a transition element, a feature previously deemed distinguishing over Cais, Anbar, and the rest of the cited art. That these points were determinative over the art is evident in the Examiner's withdrawal of the rejections based on Cais, etc., in the next Office Action, which applied different art, Houk, also later overcome.

The Office rules require examiners to avoid piecemeal prosecution. For instance, see MPEP § 707.07(g). Indeed,

[s]witching . . . from one set of references to another by the examiner in rejecting in successive actions claims of substantially the same subject matter will alike tend to defeat attaining the goal of reaching a clearly defined issue for an early termination, i.e., either an allowance of the application or a final rejection.

MPEP § 706.07.

Applicants respectfully object to the resurrection of the same grounds of rejection that have been explicitly overcome, especially as a final rejection. The present claims do not differ substantially from those that overcame the presently (and previously) cited art. Indeed, the Examiner actually repeated verbatim the majority of each renewed rejection from the previous Office Action, with no explanation as to how the subsequent amendments supposed changed the invention in support of these renewed rejections. The mere fact that that a claim has been amended does not automatically provide grounds for re-applying the previous rejections. The Examiner has provided no rebuttal to the arguments made by Applicants in the Reply filed October 31, 2007, nor any reasons for renewing the rejections that have not already been previously addressed and overcome.

Applicants therefore request that the rejections be withdrawn, or at the very least that the finality of the present Office Action be withdrawn such that Applicants have the opportunity to address any new issues raised by the Examiner.

B. Rejection under 35 U.S.C. § 102(b)

The Examiner rejected claims 1-5, 20-21 and 23-25 for alleged anticipation by Cais, USP 4,205,952, as supported by Anbar, USP 4,022,876. Applicants respectfully traverse this rejection for the same reasons made previously of record in the Replies filed February 20 and October 31, 2007, and found persuasive in the subsequent Office Action of January 11, 2008.

i. The cited references do not teach each and every element of the claimed invention

An anticipation rejection under 35 U.S.C. § 102 requires a showing that each limitation of a claim is found in a single reference, practice or device. *See In re Donohue*, 766 F.2d 531 (Fed. Cir. 1985). In order for a reference to be anticipatory, it must “be enabling and describe the applicant’s claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention.” *See In re Paulsen*, 30 F.3d 1475 (Fed. Cir. 1994). Applicants assert that the cited references do not anticipate the present claims as they do not teach each and every element of the claims.

The present claims are drawn to a kit for the detection and measurement of a positively charged transition element in a sample, where the measured transition element is a tag on a biologically active material that binds with at least one of an analyte and analyte complex, comprising at least one tag, wherein the at least one tag comprises at least one isotope of a transition element and a linker moiety, wherein the tag is capable of directly tagging a biologically active material, as well as instructions and packaging means.

On the other hand, Cais discloses tagging a biological material with a transition element and *measuring the tag with atomic absorption spectroscopy*. *See, e.g.*, col. 4, line 50; col. 5, lines 48-55; col. 7, line 1; col. 12, line 8). This method cannot detect and distinguish isotopes. A more discriminating method of detection, such as mass spectroscopy, must be used to detect the isotopes of the present invention; however, Cais specifically teaches away from using mass spectroscopy due to “various degrees of non-specificity and interferences cause that these techniques could not be practically applicable.” Col. 1, lines 28-36. Thus, Cais cannot disclose the present invention, as, instead of being merely “silent

with respect to isotopes" as alleged by the Examiner (Office Action, page 4), it specifically teaches away from using methods for detecting the isotope tag.

Anbar does not remedy this deficiency. The Examiner applies Anbar as allegedly teaching tagging biologically active material with transitional elements. Further, the Examiner states that "Anbar et al. teaches the detection of a transition element having an atomic number of 29." Office Action, page 4. This statement is incorrect. Anbar teaches the detection of *negative* ions using mass spectrometry. *See, e.g.*, col. 2, line 29 through col. 3, line 9. Specifically, Anbar states:

Examples of these isotopes, which are preferred, are the ones which are not subject to back-ground noise caused by other negative ions present in the specimen being analyzed. Preferred stable isotopes, as previously indicated, are exemplified by ^{127}I and ^{129}I if necessary, ^{81}Br , ^{36}Cl , ^{74}Se , ^{79}Se , ^{120}Te , ^{133}Te , ^{14}C , as well as tritium.

Col. 3, lines 35-40. Indeed, where the Examiner points to Anbar as allegedly teaching the use and detection of a copper ion, Anbar actually teaches the use and detection of the negative ion, iodide or selenide, *not* the copper ion, as evidenced by reading the entire sentence as follows

Still another technique is to convert a *halogen* or *chalcogen* carrying protein into an inorganic form such as copper iodide or copper selenide and introduce the latter into the mass spectrometer *negative ion source*.

Col. 4, lines 11-15, emphasis added. Copper is not being measured, but rather the negative ions. Similarly, the other passage to which the Examiner points to as allegedly teaching the use and detection of copper actually recites the use and detection of the halide to which it is bound. Col. 2, lines 35-49. The fact that copper is present is merely incidental to the negative ion assay.

In contrast, the present invention employs a tag of at least one isotope of a transition elements in a kit for the detection and measurement of a positively charged transition element. Cais cannot be used to detect isotopes, as previously discussed, and indeed teaches away from techniques that may be used to detect isotopes. Anbar teaches detection of

negative ions. Alone or in combination, these references cannot teach each and every feature of the claimed invention.

ii. The cited references were improperly combined

For a second reference to be applied in a rejections under 35 U.S.C. § 102(b), it must be offered to either (A) prove the primary reference contains an “enabled disclosure;” (B) explain the meaning of a term in the primary reference; or (C) show that a characteristic not disclosed in the reference is inherent. MPEP § 2131.01. Applicants assert that Anbar has been improperly combined with Cais for a rejection under Section 102(b).

The Examiner, in the Interview on December 4, 2008, noted that Anbar was being relied upon to show the inherency of using isotopes of transition elements for tagging biologically active materials. However, “[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.” *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). Applicants assert that the use and detection of isotopes of transition elements for tagging biologically active materials does not necessarily flow from the teachings of Cais, nor can Anbar so evidence that inherent characteristic.

As discussed above, Cais utilizes other techniques for detection, and these techniques cannot distinguish isotopes of transition elements. Anbar teaches measuring the negative ion, not the transition element. As Anbar teaches a completely different tag and technique, it cannot be combined with Cais as teaching an inherent characteristic of Cais. Thus, combining Anbar with Cais is improper.

Because Cais cannot anticipate the present claims, and because Anbar neither remedies the deficiencies of Cais nor is combinable under 35 U.S.C. § 102(b), Applicants respectfully request that the rejection be withdrawn.

C. *Rejections under 35 U.S.C. §103(a)*

The Supreme Court has recently reaffirmed the *Graham* factors for the determination of obviousness. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1739 (2007) 127 S. Ct. 1727 (2007) (holding that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions). These four factual inquiries under *Graham* are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the prior art and the claims in issue; 3) resolving the level of ordinary skill in the prior art; and 4) evaluating evidence of secondary consideration. *Graham v. John Deere*, 383 U.S. 17-18 (1966). In accordance with these factors, to establish a *prima facie* obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Applicants assert that this burden has not been met.

(i) **Maggio**

The Examiner rejected claims 6-9 over Cais as supported by Anbar, *supra*, in view of Maggio, IMMUNOENZYME TECHNIQUE I (1980), CRC Press, pp. 186-87. Applicants respectfully traverse this rejection for the same reasons made previously of record in the Reply filed October 31, 2007, and found persuasive in the subsequent Office Action of January 11, 2008.

The Examiner states that Cais as supported by Anbar differs from the claims 6-9 in not specifically teaching reagent immobilization, but alleges Maggio discloses enzyme immunoassays wherein either the antigen or antibody is immobilized onto a solid phase.

As stated above, Cais as supported by Anbar does not disclose a kit for the detection and measurement of a positively charged transition element in a sample comprising an isotopic tag for directly tagging a biologically active material with an isotope of a transition element and a linker moiety, nor instructions and packaging means. Maggio does not remedy the deficiencies of Cais as supported by Anbar. Because the prior art references do not teach

or suggest all of the claim limitations, they cannot render the present claims obvious. Therefore, Applicants request that the rejection be withdrawn.

(ii) Foster

The Examiner rejected claims 6-9 over Cais as supported by Anbar, *supra*, in view of Foster, USP 4,444,879. Applicants respectfully traverse this rejection for the same reasons made previously of record in the Reply filed October 31, 2007, and found persuasive in the subsequent Office Action of January 11, 2008.

The Examiner alleges that Foster teaches various kit configurations including standards and buffers. However, Foster cannot remedy the deficiencies of Cais as supported by Anbar as discussed above. Because the prior art references do not teach or suggest all of the claim limitations, they cannot render the present claims obvious. Therefore, Applicants request that the rejection be withdrawn.

(iii) Nielsen

The Examiner rejected claim 29 of Cais as supported by Anbar, in view of Nielsen, *Spectrochimica Acta Part B* (1998) 53: 339-45. Applicants respectfully traverse this rejection for the same reasons advanced in the Reply filed October 31, 2007, and found persuasive in the subsequent Office Action of January 11, 2008.

The Examiner alleges that Neilson discloses immunoelectrophoresis electrophoresis and laser ablation ICP-MS for the identification and quantification of metal binding proteins in blood serum. Yet, Neilson merely discloses a method to identify serum proteins that naturally bind metals (cobalt). Nielsen does not disclose the use and detection of tag comprising an isotope of a transition element and a linker moiety, as required by the present claims. The same deficiency applies to Cais as supported by Anbar, as discussed above. Because the prior art references do not teach or suggest all of the claim limitations, they cannot render the present claims obvious. Therefore, Applicants request that the rejection be withdrawn.

(iv) Crooke

The Examiner rejected claim 29 over Cais as supported by Anbar, in view of Crooke, WO 99/451,450. Applicants respectfully traverse this rejection for the same reasons made previously of record in the Reply filed October 31, 2007, and found persuasive in the subsequent Office Action of January 11, 2008.

The deficiencies of Cais as supported by Anbar, as discussed above, and Crooke cannot remedy these deficiencies. The Examiner states that Crooke discloses the use of a "plurality" of tagged transition elements and biologically active materials. The method of Crooke teaches ionization of the entire tagged biomolecule and not just the tag itself, as in the present application. Applicants' claimed invention is distinguished from the method of Crooke because only the tag comprising the isotope of a transition element is measured in the present method (not the tagged biomolecule). Since the prior art references do not teach or suggest all of the claim limitations, they cannot render the present claims obvious. Therefore, Applicants request that the rejection be withdrawn.

CONCLUSION

Applicants submit that this application is in condition for allowance, and an early indication to this effect is requested. Examiner Cook is invited to contact the undersigned directly, should she feel that any issue warrants further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 CFR §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then Applicants hereby petition for such

extension under 37 CFR §1.136 and authorize payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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